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Research Paper

Modern Radiation Further Improves Survival in Non-Small Cell Lung Cancer: An Analysis of 288,670 Patients

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Abstract

Background: Radiation therapy plays an increasingly important role in the treatment of patients with non-small-cell lung cancer (NSCLC). The purpose of the present study is to assess the survival outcomes of radiotherapy treatment compared to other treatment modalities and to determine the potential role of advanced technologies in radiotherapy on improving survival.

Methods: We used cancer incidence and survival data from the Surveillance, Epidemiology, and End Results database linked to U.S. Census data to compare survival outcomes of 288,670 patients with stage I-IV NSCLC treated between 1999 and 2008. The primary endpoint was overall survival.

Results: Among the 288,670 patients diagnosed with stage I-IV NSCLC, 92,374 (32%) patients received radiotherapy—almost double the number receiving surgery (51,961, 18%). Compared to other treatment groups and across all stages of NSCLC, patients treated with radiotherapy showed greater median and overall survival than patients without radiation treatment ($p < 0.0001$). Radiotherapy had effectively improved overall survival regardless of age, gender, and histological categorization. Radiotherapy treatment received during the recent time period 2004 – 2008 is correlated with enhanced survival compared to the earlier time period 1999 – 2003.

Conclusion: Radiation therapy was correlated with increased overall survival for all patients with primary NSCLC across stages. Combined surgery and radiotherapy treatment also correlates with improved survival, signaling the value of bimodal or multimodal treatments. Population-based increases in overall survival were seen in the recent time period, suggesting the potential role of advanced radiotherapeutic technologies in enhancing survival outcomes for lung cancer patients.

Key words: non-small cell lung cancer (NSCLC), radiotherapy, treatments, overall survival

Introduction

Lung cancer is a leading cause of cancer-related death in the United States, with non-small-cell lung cancer (NSCLC) accounting for approximately 85% of cases [1]. Over 60% of patients with NSCLC require radiotherapy at least once during their course of disease [2, 3], and radiotherapy plays an increasingly pivotal role in local tumor control and survival outcomes [4-8].

Recent years have witnessed significant advances in radiotherapeutic technology [9], with the

increasing utilization of stereotactic techniques, intensity modulated radiation therapy, 4-dimensional treatment planning, and image guidance for the treatment of stage-specific NSCLC [3, 10-14]. Aided by novel radiotherapeutic technologies, radiotherapy has made remarkable progress in achieving high local tumor control particularly in the treatment of inoperable NSCLC [15, 16]. More recently, targeted therapy and immunotherapy in combination with radiotherapy has shown promise in improving treatment outcomes and survival [3, 17-22].

In light of these developments, we hypothesized that radiotherapy treatment, facilitated by technological advances in radiation imaging, planning, and delivery, is correlated with enhanced survival outcomes. We sought to test this hypothesis through a comprehensive retrospective study of the Surveillance, Epidemiology, and End Results (SEER) data to provide insight into patterns of care and the relationship between survival and radiotherapy treatment between the years 1999 and 2008.

Methods and Materials

Data Source and Study Population

The study analyzed the SEER 17 Registry (1999–2008) from the National Cancer Institute, the comprehensive source of cancer incidence and survival data in the United States. Within SEER, we identified 288,670 patients with pathologically confirmed NSCLC between 1999 and 2008. The specific histologic types selected were adenocarcinoma, squamous cell carcinoma, large-cell carcinoma, carcinoid, and others. The use of radiotherapy, typically within 6 months of initial diagnosis, was abstracted from local tumor registries and reported to SEER. The following information was obtained and analyzed: age at diagnosis, gender, race, marital status, histology subtypes, the 5th and 6th editions of American Joint Cancer Committee (AJCC)/TNM staging category [23], SEER stage, and treatment type (radiotherapy, surgery, combined radiotherapy and surgery, or neither radiotherapy nor surgery). There was no difference in AJCC staging groups between 5th and 6th editions. Information about the use of adjuvant chemotherapy was not available within the SEER data and therefore was not included in our analysis.

Statistical Analysis

The primary endpoint of this study was overall survival (OS). The Pearson $\chi 2$ test was used to determine unadjusted associations between radiotherapy treatment and categorical variables of interest, including age, gender, stage distribution, and histology. OS was defined as the time between diagnosis and death. The Kaplan-Meier survival estimates method was used for generating the survival curves, and the log-rank test was used to assess the differences between the survival curves. Cases were also divided into two 5 year-of-diagnosis periods (1999–2003 and 2004–2008) for analysis of temporal trends. Results were considered statistically significant when P value <0.05. All P values were two-sided.

Results

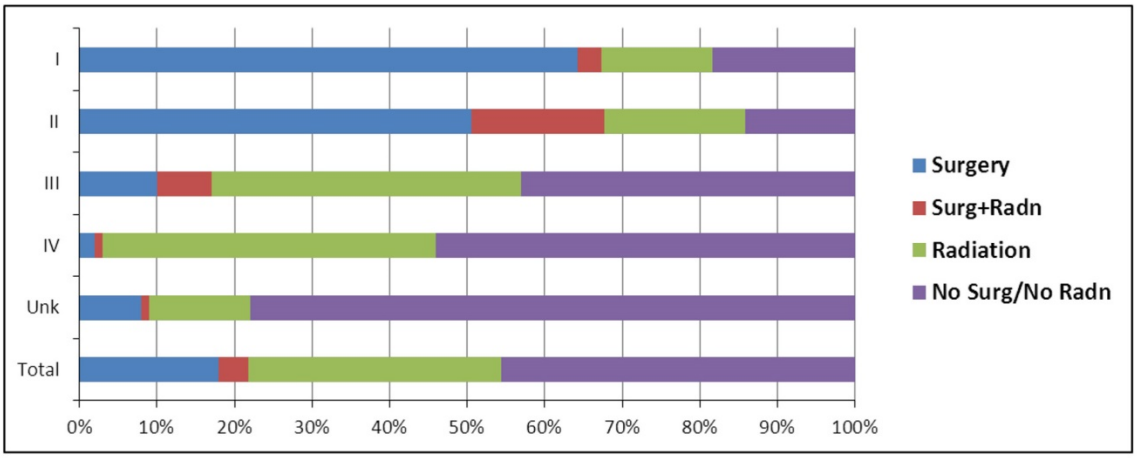
Patient Characteristics

Using the SEER database, we identified a total of 288,670 patients diagnosed with stage I–IV NSCLC between 1999 and 2008. Baseline patient, tumor, and treatment-related characteristics were provided in **Table 1**. The male to female ratio was 1.19:1. Regarding race, 238,147 (82.5%) patients were white, and 31,100 (10.8%) black. 99,495 (34.5%) patients were aged <65 years, while 189,175 (65.5%) patients were aged ≥65 years. 147,399 (51.1%) patients were married, and 129,918 (45%) unmarried. In terms of AJCC stage, 53,764 (18.6%) patients were stage I, 10,937 (3.8%) stage II, 74,570 (25.8%) stage III, and 117,228 (40.6%) stage IV. Using the SEER staging system, 51,802 (18%) patients had localized tumor, while 69,650 (24.1%) had regional tumor. In terms of histology, 98,141 (34%) had adenocarcinoma, 60,057 (20.8%) had squamous cell carcinoma, 11,669 (4.1%) had large-cell carcinoma, 115,219 (39.9%) had others, and 3,584 (1.2%) had carcinoid (Table 1).

Overall Survival and Its Associations with Patient Characteristics

The median OS for all patients (n=288,670) was 8 months. The 1-year, 2-year, 3-year, 5-year OS were 40%, 26.3%, 20.2%, and 14.5%, respectively (**Table 1; Figure 1**).

Gender, race, age, marital status, AJCC stage, SEER stage, and histology were all significantly associated with survival outcomes (**Table 1**). Young white married female patients with lower stage NSCLC had a higher median and OS. 17.2% of females had a 5-year OS, compared to 12.2% of males (P<0.0001). Patients aged <65 years had a 5-year OS of 19.6% (median survival, 11 months), while patients aged ≥65 years have a 5-year OS of 11.7% (median survival, 7 months) (P<0.0001). Stage I NSCLC had highest proportion of 5-year OS at 45.2%, with a median survival of 49 months (P<0.0001). Stage IV had the lowest proportion of 5-year OS at 2.4%, with a median survival of 4 months (P<0.0001). Five-year OS was more favorable for localized (43.5%, median survival, 45 months) than regional (19.9%, median survival, 15 months) tumors (P<0.0001).



Stage	Surgery	Surg + RT	Radiation	No Surg / No RT
I	63%	3%	14%	18%
II	50%	17%	18%	14%
III	10%	7%	40%	43%
IV	2%	1%	43%	54%
Unknown	8%	1%	13%	78%
Total	18%	4%	32%	45%

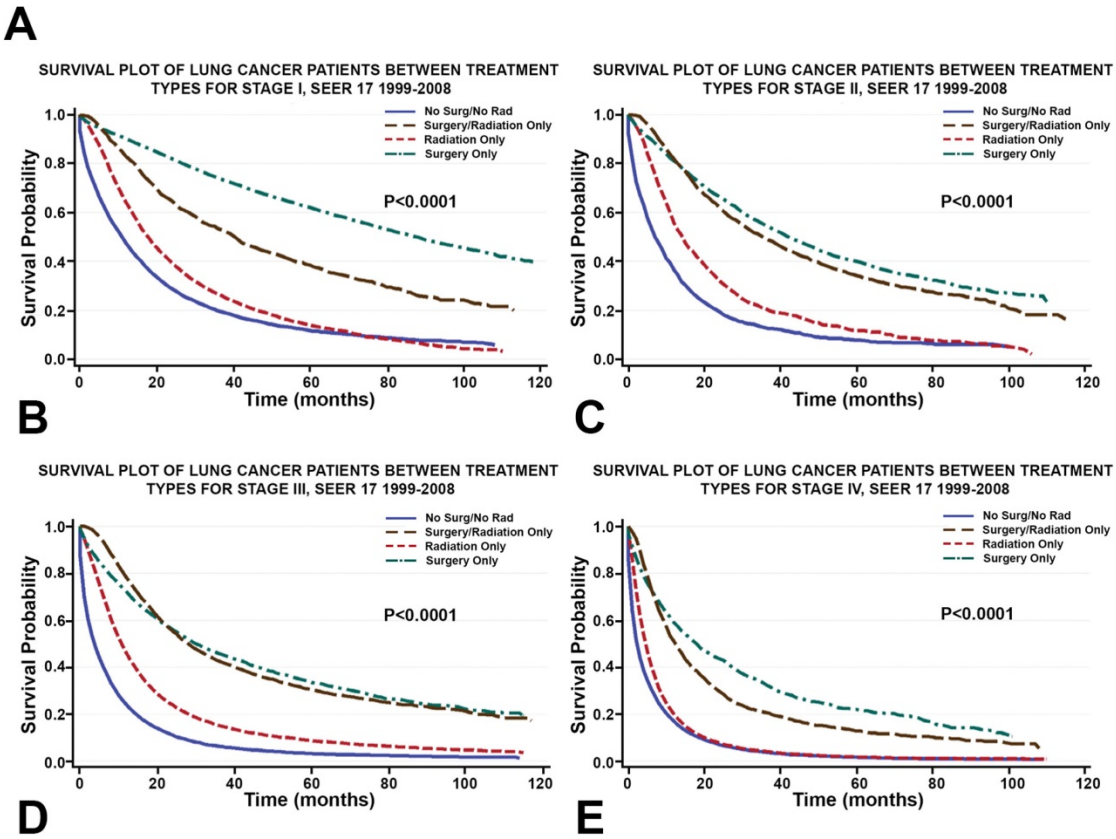


Figure 1. **A.** Among all primary NSCLC patients (n=288,670), 18% of patients received surgery, 4% combined surgery and radiotherapy, 32% radiotherapy, and 45% neither surgery nor radiotherapy. Overall, the proportion of NSCLC patients receiving radiation (32%) is almost double that receiving surgery (18%). **B-E.** Survival plots for NSCLC patients (n=288,670) between treatment types show that, across all stages, NSCLC treated with radiotherapy is associated with greater OS than NSCLC treated without surgery or radiation. While surgical treatment is correlated with the greatest OS across all stages of NSCLC, the survival distribution of combined surgery and radiation treatment begins to match that of surgery for patients with stage II/III NSCLC.

Table 1. Patient characteristics and survival.

Characteristics	# Cases	% Pts	MS (95% CI) months	% of Overall Survival (95% CI)				P Value
				1 Year	2 Year	3 Year	5 Year	
Gender								**<0.0001**
Male	156,721	54.3	7 (na, na)	36.9 (36.6, 37.1)	23.1 (22.9, 23.3)	17.3 (17.1, 17.5)	12.2 (12.0, 12.4)	
Female	131,949	45.7	10 (9,10)	43.8 (43.6, 44.1)	30.2 (30.0, 30.5)	23.8 (23.5, 24.0)	17.2 (17.0, 17.5)	
Race								**<0.0001**
White	238,147	82.5	8 (na, na)	40.1 (39.9, 40.3)	26.6 (26.4, 26.8)	20.5 (20.3, 20.6)	14.8 (14.6, 14.9)	
Black	31,100	10.8	7 (7, 8)	36.8 (36.2, 37.3)	22.3 (21.8, 22.8)	16.8 (16.3, 17.2)	11.7 (11.2, 12.1)	
Other/Unk	19,423	6.7	10 (na,na)	44.7 (44.0, 45.5)	29.8 (29.1, 30.5)	22.8 (22.1, 23.4)	15.5 (14.9, 16.1)	
Age								**<0.0001**
<65	99,495	34.5	11 (na, na)	47.0 (46.7, 47.3)	32.0 (31.7, 32.3)	25.7 (25.4, 26.0)	19.6 (19.4, 19.9)	
≥65	189,175	65.5	7 (na, na)	36.4 (36.2, 36.6)	23.3 (23.1, 23.5)	17.4 (17.2, 17.6)	11.7 (11.5, 11.9)	
Marital Status								**<0.0001**
Married	147,399	51.1	10 (na, na)	43.8 (43.6, 44.1)	29.5 (29.2, 29.7)	23.1 (22.8, 23.3)	16.9 (16.7, 17.1)	
Not Married	129,918	45.0	7 (na, na)	35.8(35.6, 36.1)	22.8 (22.6, 23.1)	17.1 (16.8, 17.3)	11.8 (11.6, 12.0)	
Unknown	11,353	3.9	8 (7, 8)	39.1 (38.1, 40.0)	25.8 (24.9, 26.7)	19.6 (18.8, 20.4)	13.9 (13.2, 14.7)	
AJCC Stage								**<0.0001**
Stage I	53,764	18.6	49 (48, 50)	78.7 (78.3, 79.0)	65.7 (65.3, 66.2)	56.9 (56.4, 57.3)	45.2 (44.7, 45.8)	
Stage II	10,937	3.8	27 (26, 29)	71.0 (70.1, 71.9)	53.3 (52.3, 54.3)	42.3 (41.2, 43.3)	29.8 (28.7, 30.9)	
Stage III	74,570	25.8	9 (9, 10)	41.7 (41.3, 42.1)	24.0 (23.7, 24.3)	16.6 (16.3, 16.9)	10.6 (10.4, 10.9)	
Stage IV	117,228	40.6	4 (na, na)	19.7 (19.5, 20.0)	8.5 (8.3, 8.7)	4.9 (4.7, 5.0)	2.4 (2.3, 2.5)	
SEER Stage								**<0.0001**
Localized	51,802	18.0	45 (44, 46)	76.7 (76.5, 77.2)	63.5 (63.0, 63.9)	54.9 (54.4, 55.4)	43.5 (43.0, 44.0)	
Regional	69,650	24.1	15 (15, 16)	55.7 (55.3, 56.1)	37.5 (37.1, 37.9)	28.5 (28.1, 28.9)	19.9 (19.5, 20.2)	
Histology								**<0.0001**
Adenocarcinoma	98,141	34.0	10 (na, na)	45.5 (45.1, 45.8)	31.0 (30.7, 31.3)	24.1 (23.8, 24.4)	17.0 (16.7, 17.3)	
Squamous Ca	60,057	20.8	10 (na, na)	44.9 (44.5, 45.3)	29.0 (28.6, 29.4)	21.9 (21.5, 22.2)	15.6 (15.3, 16.0)	
Large Cell Ca	11,669	4.1	8 (7,8)	36.5 (35.6, 37.4)	22.5 (21.7, 23.3)	17.4 (16.7, 18.2)	12.7 (12.0, 13.4)	
Carcinoid	3,584	1.2	N/A	93.8 (93.0, 94.6)	90.6 (89.6, 91.6)	87.8 (86.4, 88.8)	82.6 (81.1, 84.1)	
Others	115,219	39.9	6 (na, na)	31.7 (31.4, 31.9)	19.5 (19.2, 19.7)	14.4 (14.2, 14.6)	10.0 (9.8, 10.2)	
All Patients	288,670	100	8 (na, na)	40.0 (39.9, 40.2)	26.3 (26.2, 26.5)	20.2 (20.1, 20.4)	14.5 (14.3, 14.7)	

Note: MS=median survival, pt= patients, CI= confidence interval, ca= carcinoma, N/A= an interval that was too narrow to be computable.

Treatment Modality and Survival

Among all primary NSCLC patients, 18% of patients received surgery, 4% combined surgery and radiotherapy, 32% radiotherapy, and 45% neither surgery nor radiotherapy (**Figure 1, Table 2A, Table 2B and Table 2C**). Overall, the proportion of NSCLC patients receiving radiation (32%) was almost double that receiving surgery (18%) (**Figure 1, Table 2A, Table 2B and Table 2C**). The majority of patients with stage I/II NSCLC received surgery, whereas patients with stage III/IV NSCLC were more likely to receive radiation therapy. Combined surgery and radiotherapy was used most frequently when treating stage II NSCLC (**Figure 1, Table 2A, Table 2B and Table 2C**).

Survival plots for NSCLC patients between treatment types were shown in **Figure 1**. NSCLC treated with radiotherapy alone was associated with greater OS than NSCLC treated without surgery or radiation (**Figure 1**). While surgical treatment was correlated with the greatest OS across all stages of NSCLC, the survival distribution of combined surgery and radiation treatment begins to match that of surgery for patients with stage II/III NSCLC.

The Influence of Radiation Therapy on Overall Survival

In the patients who did not receive surgery, radiotherapy improved survival across all stages of NSCLC. The overall median survival gain was 4 months, with the most pronounced gains found in stage II/III lung cancer patients (**Table 3**). The median survival gain for stage I, II, III, and IV was 6 months, 8 months, 7 months, and 2 months, respectively. Moreover, in all patients with NSCLC, treatment with radiotherapy improved OS more than treatment without (**Figure 2**).

Radiotherapy had effectively improved OS regardless of age, gender, and histological categorization (**Table 4**).

Comparison of Overall Survival Between Time Periods

Between the time periods of 1999–2003 and 2004–2008, OS improved by 2% (**Table 4, Figure 3**). This improvement in survival outcomes is significant for patients with stage I, stage III, and stage IV NSCLC (P<0.0001, Figure 3). Among patients receiving radiotherapy (n=93,633), treatment received during the between 2004–2008 was correlated with enhanced survival compared to 1999–2003 (**Figure 3E-H**). Surgical treatment improved survival for stage

III and stage IV NSCLC (**Figure 4**). Notably, stage I NSCLC showed significant increase in survival with radiotherapy treatment but not with surgery (P<0.0001). For patients who did not receive surgery or radiotherapy (n=131,022), survival improved across every stage, suggesting that overall quality of care improved, or patient selection was favorable (**Figure 5**).

Table 2A. Radiation and survival stratified by age

Radiation		No Radiation		Radiation Difference	
MS	95% CI	MS	95% CI	*P value	MS Gain
In 151,453 patients who did not have surgery and age ≥ 65 years					
18	17, 19	10	10, 11	<0.0001	8
13	13,15	7	6, 8	<0.0001	6
10	na	3	3, 4	<0.0001	7
4	na	2	na	<0.0001	2
7	na	3	na	<0.0001	4
In 73,202 patients who did not have surgery and age < 65 years					
20	19, 22	19	17, 20	<0.0001	1
18	15, 21	9	8, 11	<0.0001	9
13	13, 14	7	7, 8	<0.0001	6
6	na	4	na	<0.0001	2
8	na	6	5, 6	<0.0001	2

Table 2B. Radiation and survival stratified by gender

Stage	Radiation		No Radiation		Radiation Difference	
	MS	95% CI	MS	95% CI	*P value	MS Gain
In 124,301 patients who did not have surgery and were male						
I	16	16, 17	10	10, 11	<0.0001	6
II	14	13, 15	7	6, 8	<0.0001	7
III	11	10, 11	4	na	<0.0001	7
IV	5	na	3	2, 3	<0.0001	2
Total	7	na	3	na	<0.0001	4
In 100,354 patients who did not have surgery and were female						
I	21	20, 22	13	12, 14	<0.0001	8
II	16	15, 18	8	7, 9	<0.0001	8
III	12	12, 13	4	4, 5	<0.0001	8
IV	5	na	3	na	<0.0001	2
Total	8	na	4	na	<0.0001	4

Table 2C. Radiation and survival stratified by histology

Stage	Radiation		No Radiation		Radiation Difference	
	MS	95% CI	MS	95% CI	*P value	MS Gain
In 43,467 patients who did not have surgery squamous cell carcinoma (SCC)						
I	16	15, 17	9	9, 10	<0.0001	7
II	13	12, 15	7	5, 9	<0.0001	6
III	11	na	5	4, 5	<0.0001	6
IV	5	na	3	na	<0.0001	2
Total	9	na	4	4, 5	<0.0001	5
In 181,188 patients who did not have surgery and had non-SCC						
I	12	19, 20	12	12, 13	<0.0001	<1
II	15	14, 17	8	7, 9	<0.0001	7
III	12	11, 12	5	na	<0.0001	7
IV	5	na	3	na	<0.0001	2
Total	7	na	4	na	<0.0001	3

Note: MS= median survival in months, CI = confidence interval, na= an interval that was too narrow to be computable.

*The P-values are for the overall difference between the time periods for each stage.

Discussion

In our analysis of 288,670 lung cancer patients treated between 1999 and 2008, radiotherapy treatment was correlated with improved OS. Notably, the number of NSCLC patients receiving radiation (32%) was nearly double that receiving surgery (16%). In an epidemiology study of cancer survivors between 2000 and 2030, Bryant et al. reports a projected increase in radiation-treated lung cancer survivors from 16–31% [24]. These numbers underscore the growing prevalence of radiotherapy in cancer therapeutics, even as the incidence rate of lung cancer declines over recent years [3, 24, 25]. The data from the current study also suggest that combined radiotherapy and surgical treatment is correlated with enhanced survival outcomes comparable to that of surgery for stage II/III NSCLC. This trend is consistent with previous studies which have demonstrated the potential for multimodal therapy to improve treatment and survival outcomes for NSCLC [26, 27].

The chronologic impact of technological advances in radiation was analyzed during two consecutive time periods: 1999–2003 and 2004–2008. The earlier time period (1999–2003) reflects the time before the full availability of advanced technologies in radiotherapy. The latter time period (2004–2008) reflects the time after the availability of advanced imaging and radiation-delivering technologies. In this study, radiotherapy treatment during 2004–2008 showed improved survival compared to 1999–2003. Interestingly, stage I NSCLC showed significant improvement in survival with radiotherapy treatment but not with surgery, possibly due to the introduction of new technologies such as stereotactic body radiation therapy (SBRT). While stereotactic radiation was first used cranially in the 1950s, SBRT became FDA approved in 2001 for extracranial treatment of tumors and quickly showed promise in the treatment of various tumor sites including the lung [28, 29]. SBRT uses multiple radiation beams to precisely deliver high doses to tumor targets in extracranial sites. Before the advent of SBRT, surgical resection was the standard treatment for stage I NSCLC, achieving 5-year survival rates of 60–70% [28]. The emergence of SBRT has improved lung cancer survival across various countries, with survival rates comparable to that of surgery [30-32]. The Netherlands, for example, has witnessed the growth of SBRT utilization in the treatment of lung cancer over the course of 10 years [33]. In a population-based study of elderly Dutch patients with stage I NSCLC, Haasbeek et al. [34] found increases in survival for patients seen between 2001 and 2009, the years encompassing the introduction and full availability of SBRT treatment.

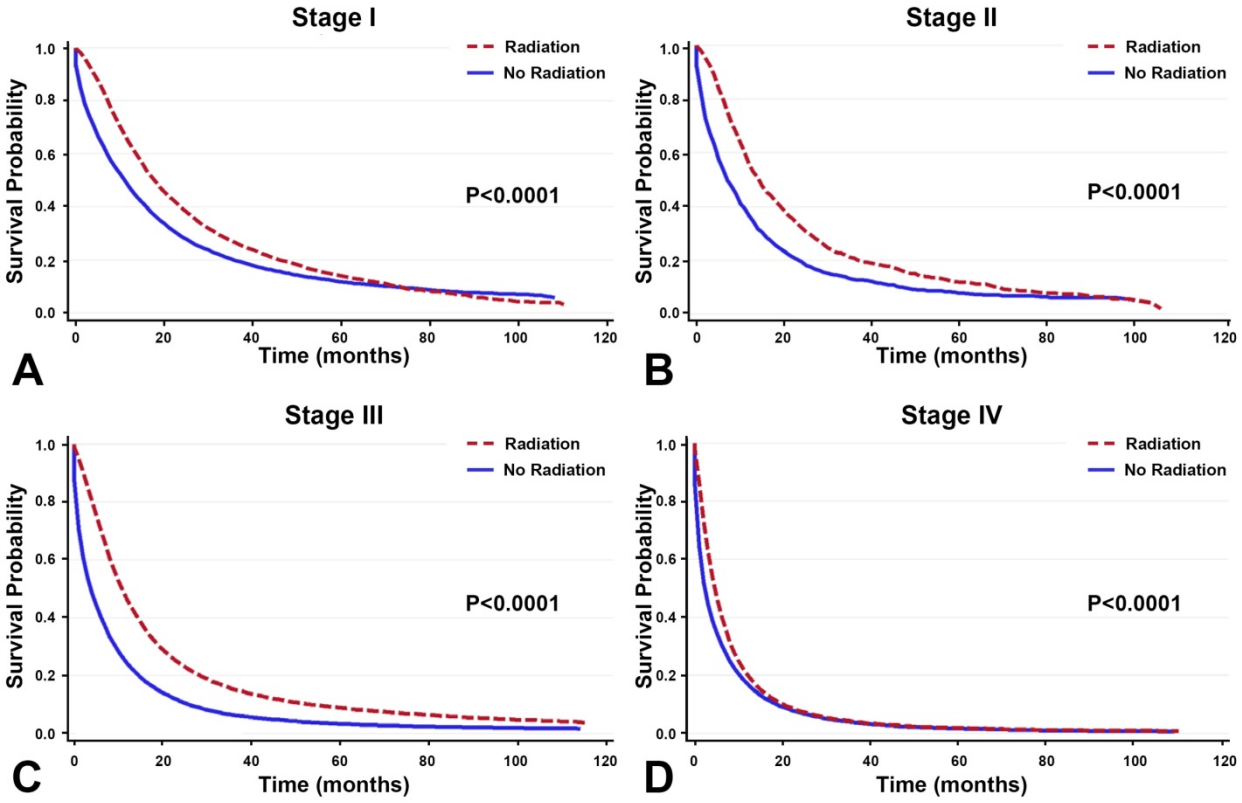


Figure 2. In the 224,655 patients who did not undergo surgery, radiotherapy is correlated with greater OS across all stages.

Table 3. Radiation improved overall survival.

Stage	Radiation			No Radiation			Radiation Difference	
	N	% pt	MS (95% CI)	N	%pt	MS (95% CI)	*P value	MS Gain (months)
I	7473	14%	18 (18, 19)	9732	18%	12 (11, 12)	<0.0001	6
II	1931	18%	15 (14, 15)	1484	14%	7 (7, 9)	<0.0001	8
III	29795	40%	11 (n/a, n/a)	31935	43%	4 (n/a, n/a)	<0.0001	7
IV	50325	43%	5 (n/a, n/a)	62865	54%	3 (n/a, n/a)	<0.0001	2
Unknown	4109	13%	12 (n/a, n/a)	25006	78%	5 (4, 5)	<0.0001	7
Total	93633	32%	8 (n/a, n/a)	131022	45%	4 (n/a, n/a)	<0.0001	4

Note: MS=median survival in months, CI = confidence interval, pt = patient, na= an interval that was too narrow to be computable.
*The P-values are for the overall difference between the time periods for each stage.
Among NSCLC patients receiving radiotherapy without surgery, radiotherapy improved median survival across all stages.

Table 4. Stage and overall survival stratified by time period.

Stage				% of Overall Survival (95% CI)			
	# Pts	% pts	MS (95% CI)	1 Yr	2 Yr	3 Yr	5 Yr
1999-2008 Total							
I	53764	19%	49(48, 50)	78.7 (78.3, 79.0)	65.7 (65.3, 66.2)	56.9 (56.4, 57.3)	45.2 (44.7, 45.8)
II	10937	4%	27 (26, 29)	71.0 (70.1, 71.9)	53.3 (52.3, 54.3)	42.3 (41.2, 43.3)	29.8 (28.7, 30.9)
III	74570	26%	9 (9, 10)	41.7 (41.3, 42.1)	24.0 (23.7, 24.3)	16.6 (16.3, 16.9)	10.6 (10.4, 10.9)
IV	117228	41%	4 (n/a, n/a)	19.7 (19.5, 20.0)	8.5 (8.3, 8.7)	4.9 (4.7, 5.0)	2.4 (2.3, 2.5)
Unknown	32171	11%	7 (6, 7)	34. 9 (34.4, 35.5)	21.4 (20.9, 21.9)	15.2 (14.7, 15.6)	9.5 (9.1, 9.9)
Total	288670	100%	8 (n/a, n/a)	40.0 (39.9, 40.2)	26.3 (26.2, 26.5)	20.2 (20.1, 20.4)	14.5 (14.3, 14.7)
1999-2003 Total							
I	27469	20%	44 (43, 46)	76.1 (75.6, 76.6)	63.3 (62.7, 63.8)	54.4 (53.8, 55.0)	43.2(42.6, 43.8)
II	4382	3%	28 (27, 30)	73.1 (71.7, 74.4)	54.2 (52.7, 55.6)	41.5 (40.1, 42.9)	30.0 (28.7, 31.4)
III	40305	29%	9 (n/a, n/a)	39.3 (38.8, 39.8)	22.1 (21.7, 22.5)	15.1 (14.8, 15.5)	9.6 (9.4, 9.9)
IV	53293	39%	4 (n/a, n/a)	17.8 (17.5, 18.1)	7.2 (6.9, 7.4)	4.1 (3.9, 4.2)	2.0 (1.9, 2.1)
Unknown	12514	9%	7 (6, 7)	33.7 (32.9, 34.5)	18.9 (18.2, 19.6)	12.3 (11.7, 12.9)	7.3 (6.8, 7.7)
Total	137963	100%	8 (n/a, n/a)	38.9 (38.6, 39.1)	25.3 (25.0, 25.5)	19.3 (19.1, 19.5)	13.8 (13.6, 14.0)
2004-2008 Total							

Stage				% of Overall Survival (95% CI)			
	# Pts	% pts	MS (95% CI)	1 Yr	2 Yr	3 Yr	5 Yr
I	26295	17%	56 (54, 58)	81.6 (81.1, 82.1)	68.6 (68.0, 69.3)	60.1 (59.4, 60.9)	NA
II	6555	4%	27 (26, 29)	69.5 (68.3, 70.7)	52.9 (51.5, 54.2)	42.2 (40.7, 43.7)	NA
III	34265	23%	10 (10, 11)	44.8 (44.2, 45.3)	26.7 (26.2, 27.3)	18.8 (18.2, 19.3)	NA
IV	63935	42%	4 (n/a, n/a)	21.6 (21.2, 21.9)	9.9 (9.6, 10.1)	5.7 (5.5, 5.9)	NA
Unknown	19657	13%	6 (6, 7)	35.9 (35.2, 36.6)	23.5 (22.9, 24.2)	18.0 (17.3, 18.6)	NA
Total	150707	100%	9 (8, 9)	41.2 (41.0, 41.5)	27.5 (27.3, 27.8)	21.3 (21.1, 21.6)	NA

Note: MS= median survival in months, CI = confidence interval, na= an interval that was too narrow to be computable.

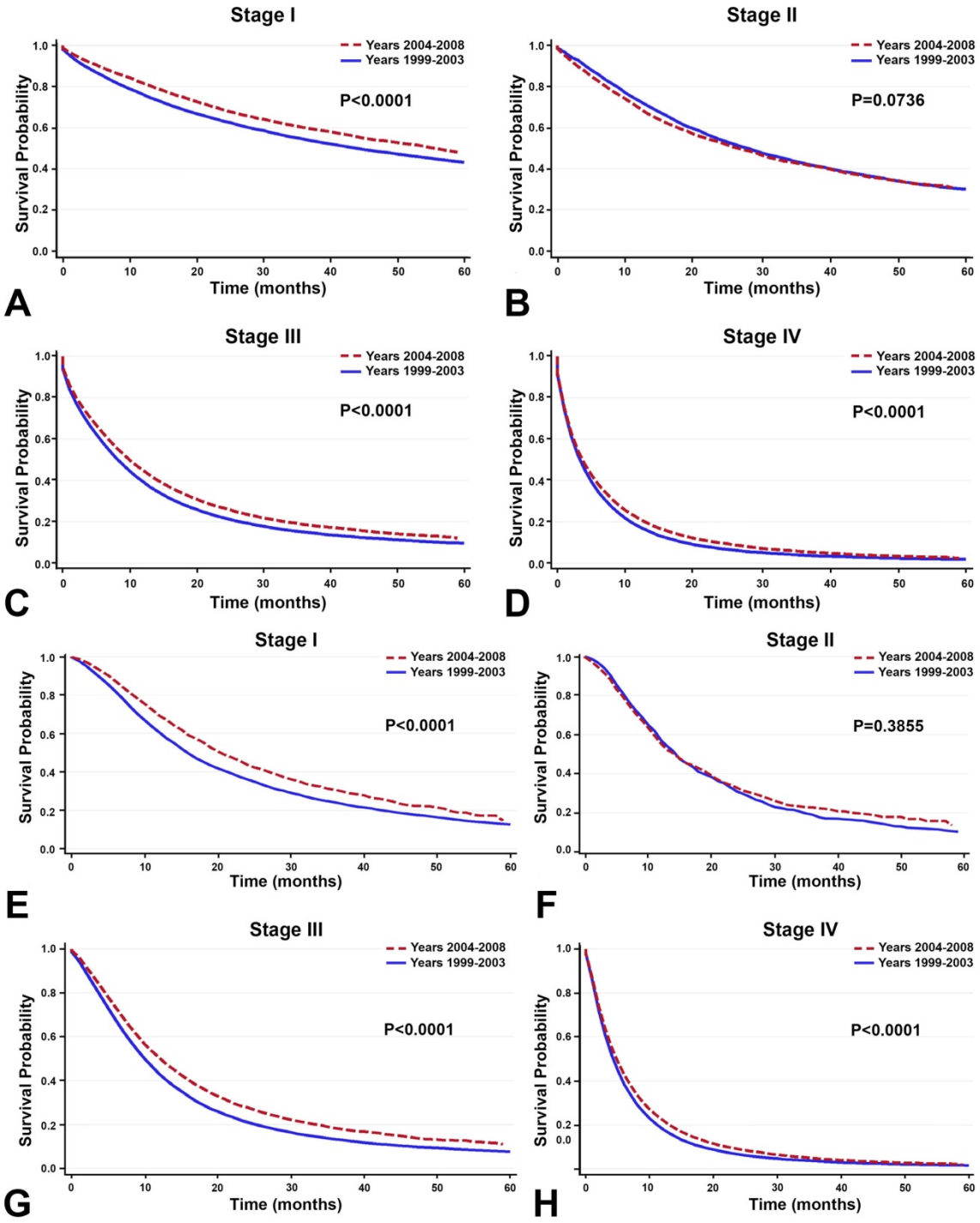


Figure 3. Survival between the time period of 1999–2003 and 2004–2008. **A-D:** Among all primary NSCLC patients (n=288,670), overall survival improved significantly for patients with stage I, stage, III, and stage IV NSCLC between the time periods 1999–2003 and 2004–2008 (*P*<0.0001). **E-H:** Among the 93,633 patients receiving radiotherapy, treatment given during the recent time period (2004–2008) is correlated with enhanced OS compared to the earlier time period (1999–2003).

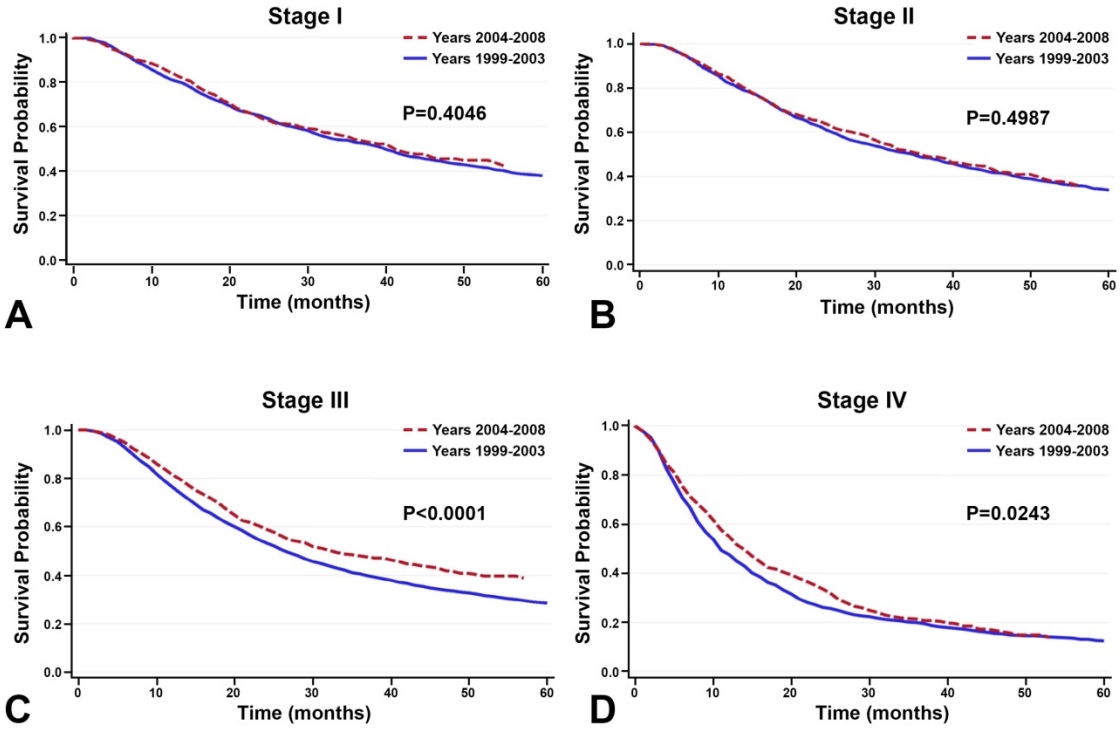


Figure 4. In the 10,838 patients receiving surgery, survival improved in the recent years (2004–2008) compared to the earlier years (1999–2003) only in stage III and stage IV NSCLC. Overall survival did not increase significantly for stage I and stage II NSCLC.

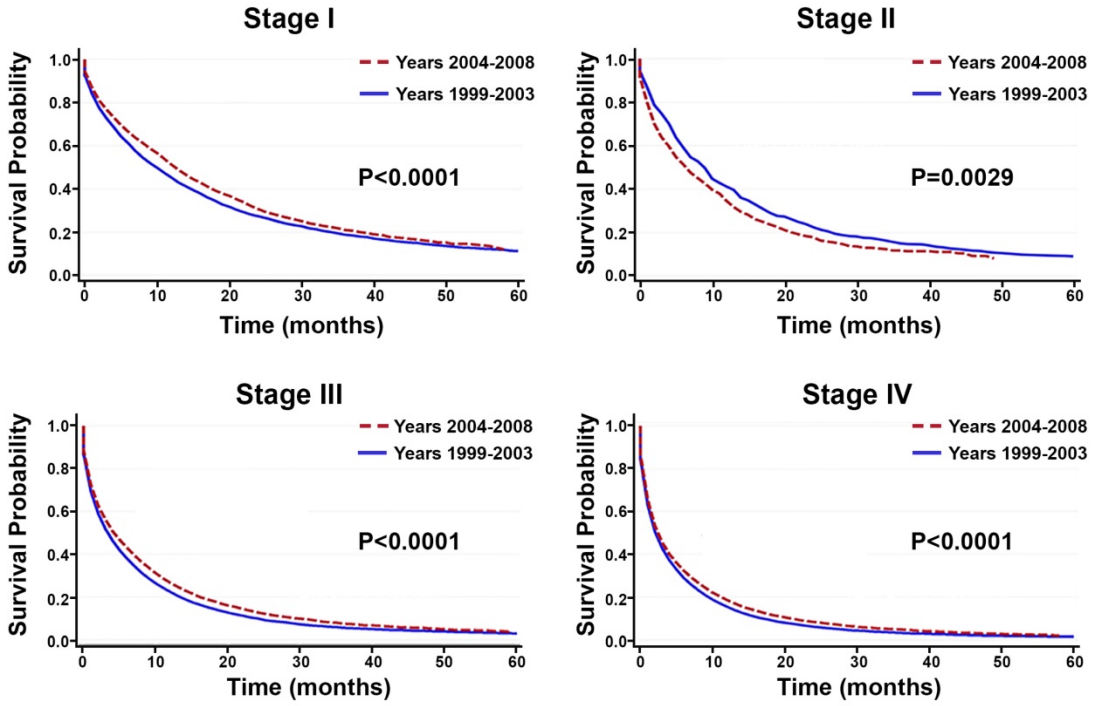


Figure 5. Among the 131,022 patients who did not receive surgery or radiotherapy, survival improved between the time periods 1999–2003 and 2004–2008 across every stage.

In the United States, the first phase I clinical trial of SBRT was conducted in 2003; Timmerman et al. [35] found that medically inoperable patients with early-stage NSCLC experienced significantly improved treatment outcomes with SBRT. In light of this encouraging data and in anticipation of widespread use of this innovative technology. RTOG236 the only SBRT multicenter trial was approved in the year of 2002, kicked off in 2003, and became widely adopted around 2004. The American

Society of Therapeutic Radiology and Oncology (ASTRO) and the American College of Radiology (ACR) developed guidelines in 2004 for integrating SBRT into the standard treatment of lung cancer [36]. Since then, numerous ongoing studies have assessed the role of SBRT in various clinical settings and have found high rates of tumor control exceeding 90% [16, 37, 38]. Indeed, our data show improved survival during this time period after implementation of the 2004 ASTRO and ACR guidelines. Improved survival may also be impacted by novel imaging techniques which could contribute to stage migration, or the Will Rogers phenomenon. Further investigation is warranted to elucidate the nuanced roles of these novel technologies [39-42].

There are several limitations to our study. SEER data were observational and retrospective, and lack information on adjuvant chemotherapy and radiotherapy technique [43, 44]. Nonetheless, the standard of care for the treatment of NSCLC is constantly evolving [45]. It is possible that, over the course of this study, patients increasingly received bimodal or multimodal treatments which could not be fully assessed in this study. Importantly, recent advancements in targeted therapy and immuno-therapy have ushered a new era of precision radiation oncology that harnesses radiobiological mechanisms and technology-driven improvements to improve therapeutic outcomes for patients with NSCLC [21, 46-48]. Combined immunoradiotherapy has shown promise in improving survival outcomes by capitalizing on the synergistic anti-tumor responses to the two treatment modalities, and several trials are underway to explore this topic [17, 18, 46-49]. Understanding the features of genomic instability that influence anti-tumor response and identifying the DNA repair biomarkers will help guide the use of immune-directed therapies combined with radiotherapy [9, 50-52]. In a phase I KEYNOTE-001 trial, radiotherapy was shown to improve progression-free survival and OS among NSCLC patients treated afterward with pembrolizumab [17]. These findings warrant further trials to more fully assess the long-term impact of radiotherapy in combination with immunotherapy[53].

Conclusions

This large population-based study of 288,670 patients with primary NSCLC shows that radio-therapy is correlated with improved survival outcomes and is increasingly utilized in the treatment of NSCLC. Our study represents one of the largest population-based studies performed to date of radiotherapy and survival in lung patients across all stages. Combined surgery and radiotherapy treatment correlate with improved survival, as compared to other treatment modalities. Our data also provide supporting evidence for the potential of recent advances in radiotherapeutic technologies to enhance survival outcomes in NSCLC. As treatment regimens evolve to utilize multimodal and targeted therapy alongside innovative technology, we enter a new era of personalized clinical oncology that promises to improve survival outcomes for patients with NSCLC through a tailored radiotherapeutic approach.

Abbreviations

NSCLC: non-small-cell lung cancer; SEER: Surveillance, Epidemiology, and End Results; (SEER); AJCC: American Joint Cancer Committee; OS: overall survival.

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Competing Interests

The authors have declared that no competing interest exists.

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